

Exhaled nitric oxide and cardiac surgery with extracorporeal circulation

To the Editor:

I read with great interest the recent publication of Humpl and colleagues¹ in the Journal and found it to contain intriguing data and several conclusions that require further clarification. In particular, I wish to comment on (1) methodologic aspects of exhaled nitric oxide (NO) measurements in patients with mechanical ventilation, (2) the anatomic origin of exhaled NO, and whether it can be used readily as a measure of endothelial dysfunction, (3) whether cardiopulmonary bypass (CPB) unequivocally causes reduction of exhaled NO, and (4) whether pulmonary blood flow influences exhaled NO in human beings. I believe that these issues are more controversial than presented in this article.

Exhaled NO is now an approved clinical diagnostic tool to monitor airway inflammation in patients with asthma; however, this approval was preceded by international consensus on methodologic aspects of exhaled NO measurements in spontaneously breathing patients. Both the European Respiratory Society and the American Thoracic Society have recognized the extreme air flow dependence of the obtained NO concentrations and have made recommendations to standardize technical aspects of the measurement to ensure comparability of data reported by different groups. Although the application of these measurements to surgical or critically ill patients with mechanical ventilation is increasing, there are currently different approaches, including real-time breath by breath monitoring, breath holding maneuvers, and, as represented by the study of Humpl and colleagues,¹ manual withdrawing of expiratory sample. This variation makes establishment of reproducibility and reference values difficult, and comparing data among different groups impossible.

Although it would be premature to conclude that real-time monitoring of expired NO in the gaseous phase, capable of resolving the NO trace throughout the entire respiratory cycle^{2,3} (Figure 1), is superior to other methods, analysis of this approach highlights a number of problems with manual withdrawal techniques. In patients with mechanical ventilation the standard expiratory flow rate (the main component of Eu-

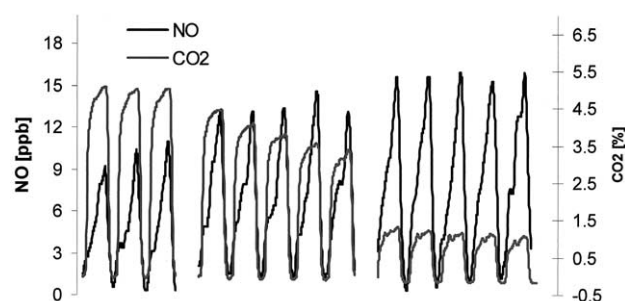


Figure 1. Representative traces depicting influence of reduction of pulmonary arterial blood flow at onset of CPB on exhaled NO and carbon dioxide (CO₂).

ropean Respiratory Society and American Thoracic Society recommendations) cannot be guaranteed, and thus the changing expiratory flow pattern produces a continuously variable concentration of NO in the gas phase (Figure 1). Studies that use real-time measurements can usually overcome this problem by calculating the area under curve or, in case of simultaneous flow measurement, by calculating NO excretion rate. It is obvious that it would require precise timing of the beginning and end of expiration by manual approaches to reproduce the accuracy of the on-line method, otherwise the data obtained would become somewhat of a lottery.

This methodologic issue appears to be crucial, because a similar study on septal defect closure by Twaretzky and coworkers (cited by the authors),⁴ which was performed by the on-line method, found an opposite response in exhaled NO. I find it somewhat disturbing that with this recognition Humpl and colleagues¹ were satisfied with averaging only two samples for each data point.

Humpl and colleagues' statement and conclusion that changes in exhaled NO levels reflect endogenous production by the pulmonary vascular endothelium¹ appears to ignore the current intense debate in the scientific community regarding the anatomic and cellular origin of exhaled NO, which is represented by studies and editorials in leading journals. In fact, the current understanding favors the hypothesis that basal exhaled NO mainly represents airway epithelial NO generation, with very little contribution from the vascular compartment and endothelium under normal conditions.⁵ This does not exclude the observations that increased endothelial NO during the application of endothelium-de-

pendent vasodilators or NO donors are capable of increasing exhaled NO under *stimulated* conditions.⁶ However, in light of recent data that effective inhibition of endothelial NO metabolism by NO synthase inhibitors (judged by increased vascular pressure) did not reduce exhaled NO in human beings,⁵ it is extremely difficult to envisage a mechanism whereby partial attenuation of endothelial NO pathways (which might indeed occur after CPB) would be reflected in exhaled NO. The likely scenario is that a decrease in endothelial NO remains undetectable by exhaled NO, and any observed change in exhaled NO likely represents events in the airway compartment, such as in the asthmatic airway.

In addition, Humpl and colleagues' discussion regarding the influence of CPB¹ appears to be a misrepresentation of the available literature data. An easy PubMed search on exhaled NO and extracorporeal circulation or CPB reveals several publications, of which at least two studies published in *The Lancet*² and *Critical Care Medicine*³ demonstrated no change in exhaled NO after CPB, and a number of studies where NO was actually increased. Thus although we all seem to agree that there are inflammatory events in the lung after CPB that are likely to involve NO, the relationship between these events and exhaled NO is not always straightforward.

Finally, Humpl and colleagues¹ concluded that exhaled NO levels are independent of changes in pulmonary blood flow. This notion can be readily disputed by data obtained during monitoring of real-time NO levels in the lower airways of intubated patients who were ventilated with standardized ventilation settings and underwent rapid changes in pulmonary artery blood

flow, such as during instrumentation of CPB. Figure 1 demonstrates that as pulmonary blood flow decreases, as evidenced by carbon dioxide delivery, exhaled NO concentrations increased. Summary data from 7 patients indicate that reduction of pulmonary arterial blood flow at the onset of CPB increases peak exhaled NO levels from 7.4 ± 1.2 ppb to 13.7 ± 1.5 ppb. These data confirm in human beings earlier suggestions that pulmonary blood flow is not required for exhaled NO, which is produced locally in the lung, and that gas-phase NO concentrations are influenced by uptake into the pulmonary circulation and blood.

Where do we go from here? This discussion highlights the fact that Humpl and colleagues¹ have undertaken a complex task in attempting to delineate the complex influence of changes from supernormal to normal pulmonary blood flow and CPB-associated partial and transient ischemia-reperfusion and systemic inflammatory response on the pulmonary release of NO from its many sources. Although exhaled NO could represent an exciting novel diagnostic tool to monitor biochemical events of crucial importance to cardiac surgery, important methodologic issues that remain.^{7,8} Moreover, even at this early stage it is obvious that there will be crucial limitations of the methodology. More controlled studies and continued dialog with international consensus and society recommendations are needed to clarify these issues in ventilated and critically ill patients. (Exhaled Biomarkers in mechanically ventilated patients [submitted ATS/ERS Project, Marczin N, Gustafsson LE, Erzurum SC, Choi AM, Risby T, and Schuberth JJ]).

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Reply to the Editor:

We thank Dr Marczin for his interest in our work¹ and the Editor for an opportunity to respond.

The first issue raised concerns the methodology of exhaled nitric oxide (NO) analysis. There are several ways to measure exhaled NO at a constant flow rate in the sedated, intubated, and mechanically ventilated patient. These include syringe aspiration sampling as performed by us,¹ tidal breathing profiles, and single-breath controlled-flow techniques.² The latter is difficult to apply outside the neonatal period. We chose the syringe aspiration sampling method because in our preliminary investigations we found it to be a robust, reproducible technique. Indeed, we confirmed the reproducibility of the method by finding similar changes after cardiopulmonary bypass in a previous study investigating exhaled NO before and after surgical closure of left-to-right shunts in children.³ In the most recent study¹ we measured exhaled NO in an identical manner in both groups of patients, which suggests that the observed differences between groups were independent of the method of NO sampling. The results of Tworetzky and colleagues⁴ are intriguing and fully discussed elsewhere.¹

The next concerns raised by Marczin are the anatomic origin of exhaled NO and

the relationship to endothelial events. Low exhalation single-breath flow rates (<50 mL/s) are characterized by most exhaled NO arising in airways by diffusion, whereas higher flows contain a larger proportion of NO arising in the distal lung.^{5,6} The syringe sampling was performed toward the end of a mechanical tidal breath, when flows are high. Thus the exhaled breath will contain a higher proportion of NO arising in the alveolar region than would a slow single-breath exhalation. We suggest that NO produced in the endothelium of the pulmonary capillary bed may enter the alveolar space and is reflected in air sampled distally. Capillary blood volume has been shown to correlate with exhaled NO.⁷ Notwithstanding the elegant study by Sartori and coworkers,⁸ which was performed in healthy adults, there is evidence to suggest that endothelial derived NO at least partly contributes to exhaled NO levels in cardiovascular disease.^{9,10} Indeed, Marczin's published position is equivocal on this subject, sometimes for¹¹ and sometimes against.

The influence of cardiopulmonary bypass on exhaled nitric oxide levels is likely to be complex and dependant on the disease, the surgical procedure performed as well as the timing of the measurements. Thus Marczin's cited examples of adults undergoing lung transplantation¹² or coronary artery surgery with bronchoalveolar lavage¹³ may not be comparable to children with congenital heart disease. Indeed, our study is perhaps unique in that cardiac correction was achieved with the use of bypass in one group and without in another. The changes in exhaled nitric oxide thus can be more certainly attributed to cardiopulmonary bypass than is possible in other studies.

The changes in pulmonary blood flow during cannulation for cardiopulmonary bypass described by Marczin are fascinating, and we are certain his group will have the opportunity to submit them for peer review. However, they are irrelevant to the investigation we undertook and to our conclusions. Stated simply, after closure of an atrial septal defect exhaled nitric oxide either increases or decreases, and it is the method of closure and sequelae (surgery vs transcatheter), rather than the hemodynamic consequence of closure (reduction in pulmonary blood flow) that influences the direction of change.